

B-Type Natriuretic Peptide A Biomarker for the Diagnosis and Risk Stratification of Patient with Sepsis and Septic Shock

NAEL S. AHMED, M.D.; AMAL RISK, M.D.; SHEREEN M. SAID, M.D. and RANDA A. MOSTAFA, M.Sc.

The Department of Critical Care Medicine, Faculty of Medicine, Cairo University

Abstract

Background: B-type natriuretic peptide (BNP) is a neuro-hormone released from the ventricles of the heart. The goal of this study was to examine the relationship between BNP levels and the severity of sepsis independent of congestive heart failure.

Design: Prospective, non randomized control study.

Setting: University Hospital, Critical Care Medicine Department from March 2010 to Feb. 2011.

Patients: Thirty patients were divided into 3 groups: 10 patients with severe sepsis and septic shock, 10 patients with early sepsis, and 10 age-matched healthy control subjects. We excluded patients with septic shock who had comorbid conditions (congestive heart failure or renal failure); sepsis severity was determined using the Sequential Organ Failure Assessment scoring system. Patients with sepsis were followed-up for 7 days.

Main Outcome Measures: Serum BNP levels, determined at the time of diagnosis of sepsis and on patient improvement or deterioration.

Results: Patients with septic shock had significantly higher BNP levels on admission compared with the other 2 groups ($p < 0.001$). Plasma BNP levels for patients with septic shock were positively correlated with Sequential Organ Failure Assessment scores and also BNP had prognostic value.

Conclusions: This study confirms the relationship between BNP level elevation and severity of sepsis independent of congestive heart failure. It also supports the utility of BNP level as a marker for mortality in septic shock.

Key Words: B-Type natriuretic peptide – Sepsis – Septic shock.

Introduction

B-TYPE Natriuretic Peptide (BNP) is a neuro hormone released from cardiomyocytes in response to increased wall stress and left ventricular dys-

function [1,2]. B-type natriuretic peptide belongs to the group of cardiac natriuretic hormones shown to have natriuretic, diuretic, vasodilator, and anti-mitogenic effects on cardiovascular tissue. Through these effects, BNP is postulated to play an important role in cardiovascular homeostasis and fluid volume regulation [3]. In patients with congestive heart failure (CHF), increased secretion of BNP partially counteracts the effects of norepinephrine, endothelin, and angiotensin II, limiting the degree of vasoconstriction and sodium retention and thus lowering the effective vascular volume and decreasing the load on the heart [4]. Furthermore, increased BNP levels have been shown to be valuable predictors of the short-term and long-term risks of cardiac dysfunction and death in many critical care setting, including acute coronary syndrome and CHF [4-9]. This led to approval for using BNP level to determine risk stratification in acute coronary syndrome and the proposal to use serial BNP measurements during patient follow-up because they may aid in prognostic assessment and determination of response to therapy [9].

Sepsis and septic shock continue to pose clinical and diagnostic challenges. Severe sepsis has been reported to cause more than 200 000 deaths per year, most of which are attributed to cardiovascular collapse [10-11]. Patients with septic shock were shown to have reversible left ventricular systolic dysfunction with an associated elevation in cardiac index [12]. It was also determined that myocardial depression in patients with septic shock until death or recovery [13]. The early assessment and diagnosis of cardiovascular dysfunction and its severity in patients with septic shock requires special equipment and expertise. Thus, a readily measurable circulating biomarker would facilitate the assessment and perhaps prevent cardiovascular dysfunction in these patients [11].

Correspondence to: Dr. Nael S. Ahmed, The Department of Critical Care Medicine, Faculty of Medicine, Cairo University

To our knowledge, Many studies have shown a relationship between an increase in BNP levels and septic shock. Other studies have examined N-terminal (NT) prohormone forms of atrial natriuretic peptide (ANP) (NT-pro ANP) and BNP (NT-pro BNP) as potential markers for sepsis. These analytes represent residual fragments of proANP and NT-proBNP may serve as useful laboratory markers of cardiac dysfunction and may help differentiate between survivors and nonsurvivors of severe sepsis [14,15].

The role of BNP during early sepsis and septic shock, specifically with regard to a correlation between BNP levels and sepsis severity independent of CHF, In light of the association of myocardial dysfunction in sepsis, there may be additional utility for BNP level in a non-CHF setting, namely sepsis. Our aim was to determine the role of BNP level as a potential marker of outcome in septic patients independent of CHF.

Patients and Methods

Thirty patients were selected for this prospective, nonrandomized control study. The patients were divided into 3 groups: 10 patients were diagnosed as having septic shock, 10 patients were diagnosed as having early sepsis, and 10 served as age-matched healthy control subjects. All septic patients cultures were taken from blood, an idewelling catheter, sputum, or a urinary source. Congestive heart failure was ruled out in included patients by results of right heart catheterization or transthoracic echocardiogram. Renal and hepatic failure were also ruled out. Patient consent was obtained from the patient, the legal guardian, or the next kin [16].

Exclusion criteria:

Excluded from our study any patient with any of the following criteria:

- Coronary insufficiency by history or ECG finding.
- Cardiothoracic trauma or surgery.
- Dilated cardiomyopathy.
- Pulmonary embolism.
- Pre-existing reduction of left ventricular function.
- Chronic renal failure.
- Chronic liver failure.

As the above conditions may be associated with an elevation of BNP.

The study group were subjected to the following:

I- Full medical history taking especially history of:

- Cardiomyopathy.
- Ischemic heart diseases.
- Arterial hypertension.
- Diabetes.
- Liver diseases.
- Smoking.
- Renal diseases.

II- Complete general examination.

III- SOFA score to determine the initial severity of the disease on admission.

IV- Base line 12-lead ECG to exclude acute ischemic event.

V- Base line arterial blood pressure and monitoring continuously.

VI- Full blood chemistry including:

- Complete blood picture on admission.
- Liver function test to detect the presence of liver dysfunction.
- Coagulation profile.
- Kidney function test including urea and creatinine.
- Arterial blood gases.
- BNP on admission, 4th day and 7th day.

VII- Echocardiography.

All patients with septic shock were admitted to the intensive care unit and all laboratory, biochemical, hemodynamic, and physical variables were determined on the day of diagnosis (day 0) and on fourth and seventh days after diagnosis.

Hemodynamic measures recorded included central venous pressure, cardiac output, cardiac index, heart rate, mean arterial pressure, body temperature, respiratory rate. The white blood cell count, platelet count, liver function were recorded.

Patients with sepsis and septic shock were stratified according to the degree of their sepsis as measured by the Sequential Organ Failure (SOFA) scale. SOFA is a reliable outcome predictor in septic shock and is a better predictor of outcome in patients with cardiovascular dysfunction than other scoring systems are [17].

Table (1): The sequential organ failure assessment score [18] (Quoted from Vincent et al., 1996).

Organ system	Score				
	0	1	2	3	4
Respiratory PaO ₂ /FiO ₂	>400	≤400	≤300	≤200	≤100
Renal Creatinine (μmol/l)	≤110	111-170	171-299	300-440 urine output ≤500 ml/d	>440 urine output <200 ml/d
Hepatic Bilirubin (μmol/l)	≤20	20-32	33-101	102-240	>240
Cardiovascular Hypotension	No hypotension	MAP <70 mmHg	Dopamine ≤5a or Dobutamine (any dose)	Dopamine >5a or epinephrine ≤0.1 a or norepinephrine ≤0.1a	Dopamine >15a or epinephrine >0.1a or norepinephrine >0.1a
Hematologic Platelet count (/mm ²)	>150	≤150	≤100	≤50	≤20
Neurologic Glasgow Coma Score	15	13-14	10-12	6-9	<6

Blood sample collection and BNP level measurement:

Blood samples for the measurement of BNP level were obtained by venipuncture and collected in EDTA tubes. The BNP level for patients with septic shock and early sepsis was determined on the day of diagnosis, fourth day and seventh day. Blood was withdrawn from the 10 controls only once.

The BNP level was measured with a single-use fluorescence immunoassay (Triage BNP Test; Biosite Inc, San Diego, California) on the manufacturers meter (Triage Meter, Biosite Inc). This system determines the concentration of BNP in whole blood or plasma using EDTA as the anticoagulant. The specimen is added to the sample port of the test device with a transfer pipette. After the specimen is added, the device is inserted into the meter, which is programmed to automatically perform the BNP analysis after the sample has reacted with the reagents (stabilizers, murine BNP monoclonal antibodies, and BNP polyclonal antibodies labeled with fluorescent dye) within the device. The BNP analysis is based on the amount of fluorescence detected; a greater amount of fluorescence indicates a higher BNP concentration in the specimen. The test should be performed within 4 hours of sample collection, otherwise, the plasma should be separated and stored at 20 C until it can be tested. The analytical sensitivity (or the lowest detectable concentration that is distinguishable from zero) for the immunoassay was determined by testing a zero calibrator 20 times each using 3

lots of reagents and 5 meters on 5 different days. The intrapatient and interpatient coefficient of variation for this test was approximately 10%. The average 95% confidence limit of the analytical sensitivity of the immunoassay was less than 5pg/ml (to convert BNP to nanograms per liter, multiply by 1) [19].

Statistical analysis:

The data are presented as mean, SD. Because most of the data were normally distributed, the *t*-test was applied. Values of $p < 0.05$ were considered statistically significant.

Results

BNP levels in patients with septic shock:

The 10 patients diagnosed as having septic shock had elevated BNP levels at the time of diagnosis (mean level 717pg/ml), which were significantly higher than those of the age-matched healthy controls (mean level 61pg/ml) $p < 0.05$. The sepsis group was further subdivided into 2 groups on the basis of patient survival and second BNP measurement was obtained 4 and 7 days after initial diagnosis. Those who improved clinically and survived ($n=3$) had elevated BNP levels although these patients had lower BNP levels on day 4 and 7 than the levels obtained on day 0, they were still significantly higher than those of control group ($p < 0.05$). The second group of patients with septic shock, who did not improve clinically within 7 days and who eventually died ($n=7$), maintained elevated BNP levels.

Levels of BNP in patients with early sepsis:

In the 10 patients diagnosed as having early sepsis, the mean BNP level was 442pg/ml at the time of diagnosis. This value was statistically significant when compared with control group ($p<0.05$). Subsequent BNP levels were also significantly different from those of the controls.

BNP and severity of sepsis in patients with septic shock:

SOFA score, and therefore the severity of sepsis, were higher in patients with sepsis compared with scores of controls and those recovering from sepsis ($p<0.05$). Our analysis demonstrated a significantly positive correlation between BNP levels and SOFA scores in our patient population ($p<0.05$). This positive correlation was consistent for late septic shock.

BNP level and prognosis in septic shock:

Morrow et al. [6] reported that elevated BNP levels in acute coronary syndrome constitute an independent predictor of new CHF and death. Our study demonstrates that BNP levels may also predict the prognosis of patients with septic shock: patients diagnosed as having septic shock whose BNP levels improved survived; those whose BNP levels remained elevated died. B-type natriuretic peptide was also positively correlated with the SOFA scoring system. This is the first report, to our knowledge, of a relationship between BNP levels, SOFA scores, and survival in patients with septic shock. Our study supports the use of serial BNP levels in intensive care unit as a reliable biomarker for risk stratification of patients with septic shock. The utility of BNP level in septic shock can be confounded by many factors. Our study demonstrates the prognostic value of BNP level in a group of patients diagnosed as having septic shock but without comorbid conditions such as CHF and renal failure. Although the mortality of patients with septic shock and comorbid conditions is high (up to 90%), our patients group in whom these factors were ruled out, may have a better survival outcome and these patients would benefit from BNP analysis.

In conclusion, we have demonstrated that BNP levels are significantly increased in patients in septic shock and may play an important role in risk stratification in these patients. Measurement of BNP level may serve as potential diagnostic and prognostic biomarkers for septic shock independent of CHF.

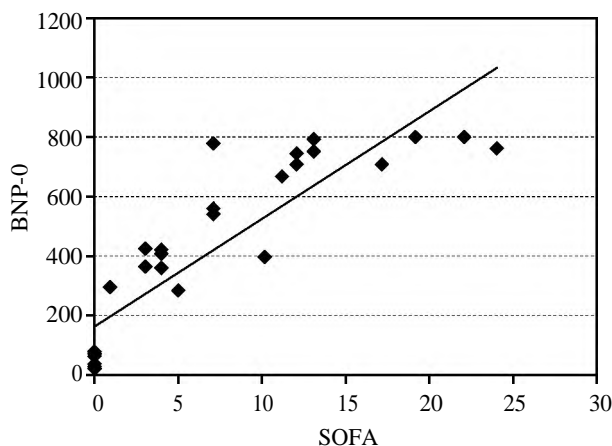


Fig. (1): Correlation between SOFA score and BNP zero day in study group-BNP between study group on zero day.

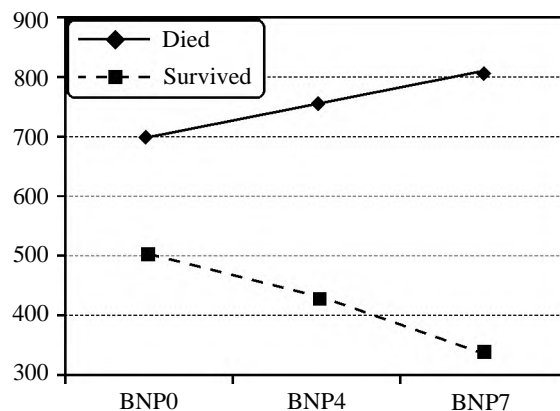


Fig. (2): BNP change between study group between survivors and non-survivors.

Table (2): Mean BNP-0 between the study groups.

	No sepsis Group I	Sepsis Group II	Severe sepsis and septic shock Group III	<i>p</i> -Value
No. of cases	10	10	10	
Mean	61.5	442.0	717.0	<0.001 (S)
SD	24.9	136.8	119.6	

S: Statistically significant difference.

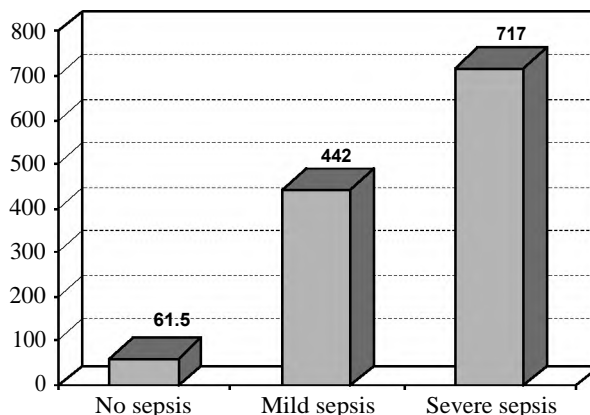


Fig. (3): Mean BNP-0 between the study groups.

Table (3): Comparison of BNP- on day 4 between mild and severe sepsis.

	Mild Sepsis	Severe Sepsis	p-value
No. of cases	10	10	
Mean	379.0	738.0	0.001 (S)
SD	160.0	141.6	

S: Statistically significant difference.

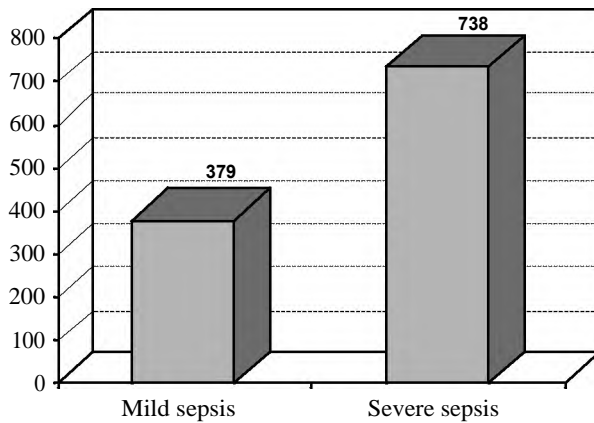


Fig. (4): Mean BNP-4 between cases with mild and severe sepsis.

Table (4): Comparison of BNP- on day 7 between mild and severe sepsis.

	Sepsis Group II	Severe sepsis and septic shock Group III	p-value
No. of cases	10	10	
Mean	331.0	720.0	0.002 (S)
SD	183.9	204.7	

S: Statistically significant difference.

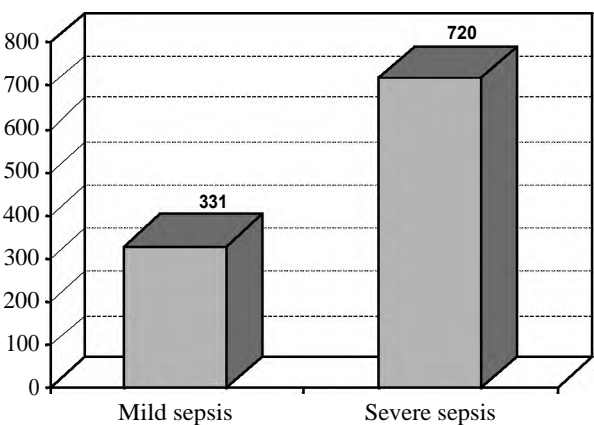


Fig. (5): Mean BNP-7 between cases with mild and severe sepsis.

Discussion

Twenty percent of our studied group showed negative cultures which is matched with Cohen et al. [20], who reported negative cultures in 39% of his patients, and also with Kieft et al. [21].

Chest infection predominated 13 out of 20 patients (65%) in both group II (sepsis) and group III (severe sepsis and septic shock), which goes with Mclean et al. [22].

Mortality rate was observed, 8 patients died out of 20 patients (40%) in both group II and group III with an average (15.4-16) days of hospital stay. These percentage goes with the results of Esmate et al. [23], 2003 who showed 55% mortality within the septic shock group, Alberti C et al. [24], 2003 documented hospital mortality ranged from 25-60% according to sepsis stage.

Ten patients diagnosed as having septic shock had elevated BNP levels at the time of diagnosis (mean level 717pg/ml), which were significantly higher than those of the age-matched healthy controls (mean level, 61.5pg/ml) this goes with Kandil et al., 2008 [25] who studied 13 pts with septic shock who had elevated BNP levels at time of diagnosis (mean level 849.4± 154.8pg/ml).

In the 10 patients diagnosed as having sepsis, the mean BNP level was 442pg/ml at the time of diagnosis. This was statistically significant when compared with that of the control group (mean 61.5pg/ml).

Our analysis demonstrated a significantly positive correlation between BNP levels and SOFA scores in our patients population. This goes with Kandil et al. [25] 2008 who found also positive correlation between BNP levels and SOFA scores.

Conclusion:

From the present study we could conclude:

- BNP correlated positively with SOFA score on admission and follow-up days.
- BNP on admission and follow-up days was higher in non-survivors that has statistical significance.
- BNP has diagnostic role in cases of sepsis and septic shock.
- BNP also has prognostic role in patients with sepsis and septic shock.

References

- 1- YAMAMOTO K. and BURNETT J.C.: Clinical criteria and biochemical markers for detection of systolic dysfunction. *J. Card Fail.*, 6 (3): 194-200, 2000.
- 2- DE LEMOS J.A., MCGUIRE D.K. and DRAZNER M.H.: B-type natriuretic peptide in cardiovascular disease. *Lancet*, 362 (9380): 316-322, 2003.
- 3- CLERICO A. and EMDIN M.: Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: A review. *Clin. Chem.*, 50 (1): 33-50, 2004.

- 4- ELSNER D., MUNTZE A., KROMER E.P. and RIGGER G.A.: Effectiveness of endopeptidase inhibition in congestive heart failure. *Am. J. Cardiol.*, 70 (4): 494-498, 1992.
- 5- DELEMOS J.A., MORROW D.A., BENTLEY J.H., et al.: The prognostic value of B-type natriuretic peptide in patients with acute coronary syndrome. *N. Engl. J. Med.*, 345 (14): 1014-1021, 2001.
- 6- MORROW D.A., DE LEMOS J.A., SABATINE M.S., et al.: Evaluation of B-type natriuretic peptide for risk assessment in unstable angina.
- 7- OMLAND T., AAKVAAG A., BONARJEE V.V., et al.: Plasma brain natriuretic peptide as an indicator of left ventricular dysfunction and long term survival after acute myocardial infarction, 93 (11): 1963-1969, 1996.
- 8- OMLAND, DE LEMOS J.A., MORROW D.A., et al.: Prognostic value of N-terminal pro-atrial and pro-BNP in patients with acute coronary syndrome. *Am. J. Cardiol.*, 89 (4): 463-465, 2002.
- 9- SLIVER M.A., MAISEL A., YANCY C.W., et al.: BNP Consensus Panel, 2004.
- 10- MORROW D.A. and BRAUNWALD E.: Future of biomarkers in acute coronary syndromes moving toward multimarker strategy, 2003.
- 11- CASTILLO J.R., ZAGLER A., CARRILLO-JIMENEZ R. and HENNEKENS C.H.: BNP a potential biomarker for mortality in septic shock, 2004.
- 12- PRICE S., ANNING P.B., MITCHELL J.A. and EVANS T.W.: Myocardial dysfunction in sepsis and therapeutic application.
- 13- COURT, KUMAR A. and PARRILLO J.E.: Clinical review: Myocardial depression in sepsis and septic shock, *Crit. Care*, 6 (6): 500-508, 2002.
- 14- WITTHAUT R., BUSCH C., FRAUNBERGER P., et al.: Plasma natriuretic peptide and BNP are increased in septic shock. *Intensive Care Med.*, 2003.
- 15- HOFFMANN U., BRUECKMANN M., BERTSCH T., et al.: Increased plasma levels of NT- pro ANP and NT-pro BNP as marker of cardiac dysfunction in septic patients, 2005.
- 16- BRUECKMANN M., HUHLE G., LANG S., et al.: Prognostic value of plasma NT-pro BNP in patients with severe sepsis, 2005.
- 17- BONE R.C., BALK R.A., CERRA F.B., et al.: Definitions of sepsis and organ failure, *Chest*, 1992.
- 18- VINCENT J.L., MORENO R. and TAKALA J.: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intens. Care Med.*, 22: 707-10, 1996.
- 19- American College of chest physicians/society of critical care medicine consensus conference, 1992.
- 20- COHEN J. and ABRAHAM E.: Microbiological findings and correlations with serum tumor necrosis factor-alpha in patients with severe sepsis and septic shock. *J. Infect. Dis.*, 180 (1): 116-21, 1999.
- 21- KIEFT H., HOEPELMAN A.I., ZHOU W., et al.: The sepsis syndrome in a Dutch university hospital. Clinical observations *Arch. Intern. Med.*, 153: 241-2247, 1993.
- 22- MCLEAN A.S., HUANG S.J., HYAMS S., et al.: Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock. *Crit. Care Med.* Apr., 35 (4): 1019-26, 2007.
- 23- ALBERTI C., BRUN-BUISSON C., SURGERY V., et al.: Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. *Am. J. Respir. Crit. Care Med.*, Vol 168: pp. 77-84, 2003.
- 24- ESMATE A., ABDEL FATTAH A. and RIZK A.: C reactive protein in view prognosis in sepsis. Master thesis Critical Care Department, Cairo University, 2003.
- 25- KANDIL E., BURAK J., SAWAS A., et al.: B-type natriuretic peptide: A biomarker for the diagnosis and risk stratification of patients with sepsis and septic shock. *Arch. Surg.* Mar., 143 (3): 242-6, 2008.